REMARKS/ARGUMENTS.

Claim 1 has been amended to limit Y^1 to $-(CH_2)_w-(C{=}O)-Z$ and the imaging moiety being attached at the Y^1 position. Support for that amendment may be found at page 8, lines 18 to 22 of the specification.

Claim 1 has been amended to limit the positron-emitting radioisotope to ^{18}F. Support for this amendment may be found at page 6, lines 23 to 26 of the specification. Claim 2 has consequently been withdrawn. Claims 1, 4, 6, 16-17, 19, 21, 29-31 and 33 are therefore now pending in the application.

1. 35 USC §103 (OBVIOUSNESS) REJECTIONS.

1.1 Sahagan.

Claims 1-2, 4, 6, 16-17, 19, 21 and 29-30 continue to stand rejected as obvious over the teachings of Sahagan (EP 1088550 A1). Applicants respectfully traverse this rejection for the reasons that follow.

Applicants refer to revised claim 1, where the location of the 'imaging moiety' is now limited to Y^1. Sahagan defines the Q group of Formula I therein (page 4) at page 5, line 50 to page 6, line 2. Sahagan explicitly states that for Q, the aryl groups may have F, Cl, Br or other substituents (page 6, lines 1 to 2 therein). Sahagan defines the 'A' group of Formula I therein at page 4 line 23 to page 5 line 10. Applicants stress that the 'A' group is defined by Sahagan differently to Q, so that halogen substituents are not contemplated at the A group therein.

Consequently, applicant's position is that Sahagan does not teach or suggest an ^{18}F radiolabel at the 'A' position – corresponding to Y^1 of present claim 1. All the teaching of Sahagan towards attachment of a halogen is at the Q, X^1 or X^2 positions of Formula I therein – not 'A'. Hence, Sahagan actually appears to teach away from the subject matter of present claim 1.

Furthermore, applicants note that the Examiner suggests that the present claims are to compounds, not a "method of imaging." Applicants respectfully point out that present claim 1 is in fact to: "A PET or SPECT imaging agent which comprises…" [emphasis added]. The

structure recited in the claim relating to the "imaging moiety," which is either a radioactive metal ion, a gamma-emitting radioactive halogen or ^{18}F, makes the claimed compounds PET or SPECT imaging agents. In sum, Applicants submit that claim 1 is not a *per se* compound claim. Rather, it is implicit in such subject matter that the agent must be in a form suitable for PET or SPECT imaging. That imposes additional constraints over a "compound" claim, so is not the same. The Examiner is therefore invited to withdraw the previous characterization of applicant's claims. Applicant's previous arguments submitted 25 March 2010 on the fact that Sahagan is silent on *in vivo* imaging are therefore believed relevant to patentability, and need to be taken into consideration.

The Examiner asserts on page 4 of the Office Action that Sahagan teaches the use of isotopically-labelled compounds in "tissue distribution studies." Applicants can find no basis for such a characterization of Sahagan. The phrase "tissue distribution" occurs only once in Sahagan – at [0043], where it refers explicitly to "…drug and/or substrate tissue distribution assays…" [emphasis added]. *See* Sahagan page 10, lines 34-36. Applicant's position is that the Examiner cannot ascribe a teaching to a document which cannot be found unambiguously within the document itself. In particular, the Examiner cannot divorce the term "assays" from this clear teaching of Sahagan.

The Examiner goes on to equate the "tissue distribution assays" of Sahagan to the "tissue distribution studies" of Pochapsky [emphasis added], and to assert that Pochapsky constitutes evidence that PET and SPECT imaging equate to "tissue distribution assays" – referring to page 231 paragraph 2 and the title of Pochapsky.

Applicants point out that the title of Pochapsky does not, in fact, include the phrase "tissue distribution assay" as alleged by the Examiner. Pochapsky does not refer to "tissue distribution assays," in particular does not use the term "assay" in the context of the biological studies carried out with the ^{18}F-labelled fatty acids described therein. Pochapsky refers instead to "tissue distribution," "tissue distribution studies" or "biodistribution studies." *See*, *e.g.*, Pochapsky at:

Title;

Abstract;

page 237 right hand column;

page 240 left hand column plus tables I to IV;

page 241 left hand column at "Discussion" first sentence.

Applicant's position is therefore that the Examiner has mischaracterized Pochapsky – and that reference does not, in fact, teach that PET and SPECT imaging equate to "tissue distribution assays".

Applicants contend that biodistribution studies of a radiopharmaceutical (as those of Pochapsky cited) are principally focused on determining the biodistribution of the radioactivity associated with the PET or SPECT imaging agent, to establish:

> (i) the feasibility of imaging the organ or site of interest *in vivo* (whether there is sufficient uptake compared to background to obtain an image, etc.);
> (ii) whether the biological behavior of the radiolabelled compound (in this case a fatty acid) reflects that of the unlabelled compound. That is always a concern, when the radioisotope is not an intrinsic part of the molecule (as is the introduction of fluorine as ^{18}F into the fatty acids of Pochapsky), and hence may change the biological characteristics. Furthermore, if the radioisotope does not remain attached *in vivo* but becomes free, then it no longer provides an image which reflects the distribution of the labelled compound;
> (iii) safety, i.e. to establish if there is any unexpected accumulation of the radioisotope in radiation-sensitive organs, because the administered radioisotope presents a potential hazard to the patient.

The focus of such "studies" is the radioactivity, i.e., establishing the fate of the radioisotope *in vivo*, in whatever chemical form the radioisotope may be. That is because it is only the radioisotope, not the compound itself, which provides the radioactive emissions which are, in turn, captured by a camera suitable for SPECT or PET imaging. With respect to point (i) above, applicants point out that the person skilled in the art would know that it may require only a minute amount of a drug to reach the desired site *in vivo* to achieve the desired effect. That logic does not hold true for medical imaging, where the amount of radioisotope in the site of interest relative to the amount in the background is crucial – otherwise an adverse signal-to-background radio may render the imaging impractical.

Applicants note also that the problem of metabolic loss of radiolabel *in vivo* alluded to in (ii) above, is something that Pochapsky *et al* report and discuss – see eg. Abstract last 3 sentences and Conclusion (page 243) therein.

The "drug and/or substrate tissue distribution assays" of Sahagan are instead directed at the drug and/or the substrate, not the radioisotope. Sahagan is not concerned with the suitability for imaging, the radiological safety or other features of a radiopharmaceutical imaging agent - since Sahagan is silent on imaging. Sahagan describes *in vitro* assays at length, from [0054] to [0114]. Sahagan is concerned to establish *in vitro* the effect of the metalloproteinase inhibitor compounds on various metalloproteinase enzymes (MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 at least) – see [0054] therein. Although the Examples of Sahagan relate only to *in vitro* studies, applicants contend that the person skilled in the art would understand the "drug…tissue distribution assay" referred to in [0043] of Sahagan, to mean equivalent assays *in vivo*. The person skilled in the art would understand that to mean the effect of the drug on the same metalloproteinase enzymes *in vivo*. That does not constitute PET or SPECT imaging. Applicant's position is therefore that PET or SPECT imaging cannot be equated to the "drug distribution assays" of Sahagan.

The obviousness rejection to claim 1 based on Sahagan should therefore be withdrawn. Claim 4, 6, and 16-17 depend on claim 1 and are hence believed, by definition, also non-obvious over Sahagan. Independent claim 19 refers to claim 1, and therefore contains all the essential features thereof. Hence, claim 19 and dependant claim 21 are also believed non-obvious over Sahagan. The same logic applies to kit claim 29 and dependant claims 30-31 and 33.

For the reasons set forth above, Applicants respectfully request that the obviousness rejection based on Sahagan be reconsidered and withdrawn.

1.2 Sahagan and Wilbur.

Claims 1-2, 4, 6, 16-17, 19, 21 and 29-30 continue to stand rejected as allegedly obvious over Sahagan in view of Wilbur [Bioconj.Chem., 3(6), 433-470 (1992)].

The Examiner's objection is based on the logic that PET and SPECT imaging equate to "tissue distribution assays". This point has been addressed at length in 1.1 (above). The

logic is believed to be invalid. In addition, the limitation of the radiolabel to the Y^1 position for Formula I in present claims is a feature which is neither taught nor suggested by Sahagan or Wilbur. Hence, no combination of those references could provide that subject matter.

For at least these reasons, Applicants respectfully request that the obviousness rejection over Sahagan and Wilbur be reconsidered and withdrawn.

1.3 Sahagan, Wilbur and Fruchtel.

Claim 33 stands rejected as being obvious over Sahagan in view of Wilbur, and in further view of Fruchtel.

The Examiner argues here that the compounds, methods and kits are already obvious from Sahagan/Wilbur, and that the additional feature of claim 33 is available in an obvious manner from Fruchtel.

Applicants contend that this argument is no longer valid, since claims 1, 4, 6, 16-17, 19, 21 and 29-31 are in fact non-obvious over the prior art for the reasons set forth above. The obviousness objection to claim 33 should therefore be reconsidered and withdrawn.

2. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION.

Claims 1-7, 12, 14-19, 21, and 29-33 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting (ODP) as being unpatentable over claims 1-29 of co-pending Appl. Ser. No. 10/544,945.

Applicants understand that the rejection over the '945 application is a "provisional" double patenting rejection and that the Patent Office will continue to make this rejection so long as there are conflicting claims in more than one application, unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications. *MPEP* § 804. Applicants also understand that if a "provisional" non-statutory ODP rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. *Id.*

Since no claims in either application have yet been held allowable, Applicants respectfully ask the Patent Office to at least hold this rejection in abeyance until the claims in the instant application have been agreed to be otherwise allowable.

In view of the above remarks, entry of the foregoing and prompt and favorable consideration of the subject application on the merits are respectfully requested.

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